REMARKS

Claims 19 and 30 are amended to recite that the claimed host cells are isolated. Support for these amendments can be found, for example, at paragraph [0291] through [0296] of the specification and in the claims as originally filed. No new matter was added by the amendments.

Claims 4-6, 11-14 and 16-31 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed July 25, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

Claims 4, 5, 14 and 16-31 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO states that the claimed nucleic acids are not enabled for nucleic acids with 95 or 99% sequence identity to SEQ ID NO: 113, or those which hybridize to such because there is no structural or functional information provided in the specification. The PTO states that there is insufficient guidance regarding how to make PRO1446 polynucleotide variants. The PTO also states that the hybridization under moderately stringent conditions would yield nucleic acid molecules that are structurally unrelated.

The pending claims are to nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO:113 or its the full-length coding sequence, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, and wherein the nucleic acid is "more highly expressed in normal stomach compared to stomach tumor" or "hybridizes to the complement of a nucleic acid of SEQ ID NO: 113" under the specified stringent conditions. Other claimed nucleic acids are those which hybridize to the recited sequences under stringent conditions.

Applicants submit that the claimed nucleic acids are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences related to SEQ ID NO: 113. Likewise, Applicants have disclosed how to determine if the claimed nucleic acids are differentially expressed in stomach tumors compared to normal stomach tissue (*see, e.g.,* Example 18 beginning at paragraph [0529] of the specification). Finally, it is well-known in the art how to determine if a nucleic acid hybridizes to the disclosed

sequences under the specified stringent conditions. Thus, one of skill in the art would know how to make the claimed nucleic acids.

The PTO asserts that "there is no way of knowing which, if any variants would have the same property of higher expression in the specific tissue." Office Action at 5. However, the specification provides specific guidance and exemplifies how to determine the expression of nucleic acids in tissues. For example, the specification teaches differential expression experiments, and the results of the experiments revealed that in stomach, the nucleic acid encoding PRO1446 was underexpressed for tumor relative to normal (Example 18, paragraph [0530]). Further, the specification teaches, for example, at paragraphs [0311] and [0449]-[0452] (Example 5), various methods for using the claimed nucleic acids in hybridization assays of samples. Thus, in view of the teachings in the specification and the knowledge in the art, one skilled in the art would be able to determine differential expression of the claimed nucleic acids.

The PTO also alleges that "hybridization under moderately stringent conditions would yield nucleic acid molecules that are structurally unrelated." Office Action at 5. No evidence is provided to support this assertion. Accordingly, this assertion represents official notice without documentary evidence. Since the structural variation of nucleic acids that hybridize to a target under moderately stringent conditions is not common knowledge or well-known, Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001). Furthermore, the relevance of the PTO's position is uncertain, because the claims do not recite "moderately stringent conditions."

Applicants submit that one skilled in the art also would know how to use the claimed nucleic acids. The PTO has recognized the fact that the claimed nucleic acids are useful as tumor markers, stating "Applicants assertion that the differentially expressed message can be used as a diagnostic tool for stomach tumor is found to be persuasive." Office Action at 3. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed nucleic acids as diagnostic tools. For example, nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences and are "more highly expressed in normal stomach compared to stomach tumor" can be used as diagnostic tools since the claimed nucleic acids are themselves differentially expressed in certain tumors. A claimed nucleic acid which has at least 95% or 99% sequence identity to the disclosed sequences and "hybridizes to the complement of a nucleic acid of SEQ ID NO: 113," or which hybridizes to the disclosed

sequences under the specified stringent conditions can be used as a hybridization probe to detect the expression of the PRO1446 gene, making it useful as a diagnostic tool. Given the skill in the art and the disclosure of how to make and use the claimed nucleic acids, Applicants request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

In sum, methods of making nucleic acids are routine in the art. One skilled in the art could readily determine the expression or hybridization properties of nucleic acids with the recited nucleic acid sequence identity. The claimed nucleic acids have utility as diagnostic tools, as acknowledged by the PTO. The specification provides guidance on methods for using the claimed nucleic acids. Accordingly, it would be routine for one skilled in the art to make and use the claimed nucleic acids. Given the skill in the art and the disclosure of how to make and use the claimed nucleic acids, Applicants request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 4, 5, 7, 14 and 16-31 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the specification does not describe all nucleic acids of the claimed genus or a representative number thereof, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the

amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 113, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, with the functional recitation as amended: "more highly expressed in normal stomach compared to stomach tumor" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO: 113" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure,

other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules.* The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. The common element or attribute of the claimed genus is that species of the genus are

structurally related to SEQ ID NO: 113, such that they hybridize to SEQ ID NO: 113 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 113 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

The PTO states that because the specification does not describe all nucleic acids of the claimed genus or a representative number thereof, the claims fail the written description requirement. No further reasoning is provided for the rejection of claims reciting specific high stringency hybridization conditions. In rejecting a claim, the PTO must set forth express findings of fact which support the lack of written description conclusion; these findings should establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. MPEP §2163.04 I. Aside from asserting that the specification does not describe all nucleic acids of the claimed genus or a representative number thereof, the PTO makes no findings of fact, nor provides any reasoning for the rejection of claims reciting specific high stringency hybridization conditions. The PTO is silent regarding what would constitute a representative number of species to sufficiently support claims reciting 95% or 99% sequence identity. The PTO is silent regarding why the specification does not convey to one skilled in the art that Applicants possess nucleic acids that can hybridize to the recited nucleic acids under the recited hybridization conditions. The PTO is silent regarding why Applicants' previous arguments relying on *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002) and Example 9 of the written description training materials are inapplicable to Applicants' claims reciting specific high stringency hybridization conditions. In short, no fact and no reasoning is provided for rejecting these claims. Accordingly, no *prima facie* case has been established to reject Applicants' claims reciting specific high stringency hybridization conditions.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***
>
> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

Given the degenerate nature of the genetic code, a large polypeptide is encoded by a vast number of different nucleic acid sequences. Yet the Court did not require the Applicants in *Wallach* to actually make and individually describe all of the sequences which encode the disclosed polypeptide sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could envision the detailed chemical structure of all or a significant number of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the polypeptide sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO: 113, and claim nucleic acids which are homologous to it and have the functional limitation of hybridizing to the disclosed sequence under the specified stringent conditions. It is routine in the art to create nucleic acids which have at least 95% or 99% sequence identity to SEQ ID NO: 113 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the knowledge in the art to determine which nucleic acids will hybridize to the disclosed sequence under the specified

conditions. This structure/function combination of a disclosed sequence and specified stringent condition is sufficient to describe the claimed nucleic acids. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus, or be able to visualize their detailed chemical structure, to adequately describe the genus.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO: 113 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in normal stomach compared to stomach tumor" are also adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants, and the applicant would not know if a particular variant possessed the requisite catalytic activity until the variant was tested.

Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in stomach tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which were attached as Exhibits 15-20 in the Response mailed May 6, 2005.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 113, by specifying the high stringency conditions under which hybridization occurs, and by describing

the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(e) – Anticipation

The PTO rejects Claims 1-10 and 12-20 as anticipated under 35 U.S.C. § 102(e) by Lal *et al.* (WO 00/00610 A2; hereinafter Lal), which was published on January 6, 2000, and by Jacobs *et al.* (WO 00/09552 A1; hereinafter Jacobs), which was published on February 24, 2000. The PTO states that Lal discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 114 of the instant invention, hybridization probes, vectors, and host cells. The PTO states that Jacobs discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 114 of the instant invention, hybridization probes, vectors, and host cells.

Lal was filed as an international patent application on June 25, 1999. Jacobs was filed as an international patent application on August 13, 1999. These publications of international patent applications do not have a prior art date under 35 U.S.C. 102 (e)(1) because the applications were filed prior to November 29, 2000. See MPEP §2136.03II(C)(2) (If international applications have an international filing date prior to November 29, 2000, "**never apply these references under 35 U.S.C. 102(e)**." emphasis added). Accordingly, these references are not properly cited as prior art under 35 U.S.C. § 102(e). Thus, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §102(e).

Even if these publications were cited as references according to their respective publication dates, these publications would not be prior art to the claimed subject matter. Applicants claim priority under 35 U.S.C. § 120 to PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 USC §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 USC §119 to US Provisional Application 60/101475 filed 9/23/1998. The PTO has

recognized that the presently claimed subject matter is entitled to a claim of priority to PCT Application PCT/US00/23328 filed 8/24/2000. The sequences of SEQ ID NOs: 113 and 114 were first disclosed in US Provisional Application 60/101475 filed 9/23/1998 in Figures 1 and 2A-B. US Provisional Application 60/101475 also disclosed, *inter alia*, the results of computer analyses of SEQ ID NOs: 113 and 114 (see, for example, page 37 of US Provisional Application 60/101475).

Lal was published on January 6, 2000, and by Jacobs was published on February 24, 2000. These dates are well after Applicants' first application disclosing SEQ ID NOs:113 and 114. Neither Lal nor Jacobs disclose any experimental results correlating SEQ ID NO:255 and SEQ ID NO:133, respectively with any particular disease. Lal and Jacobs appear to provide no more than computer analyses of the respective sequences (Lal, pages 100-101 and 116; Jacobs, page 320). Thus, Applicants maintain that they were in possession of so much of the invention as is disclosed in Lal and Jacobs prior to the publication date of those applications.

The well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention."

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need not be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need not have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (*Id.* at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited reference. Because Applicants demonstrated, by means of the disclosure in their provisional application filed September 23, 1998, that they were in possession of so much of the claimed invention as is disclosed in the Lal and Jacobs publications prior to their respective publications dates of January 6, 2000 and February 24, 2000, Applicants respectfully submit that this patent is not available as prior art.

Accordingly, Applicants submit that Lal and Jacobs are not effective prior art to the claimed nucleic acids.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 23, 2005

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